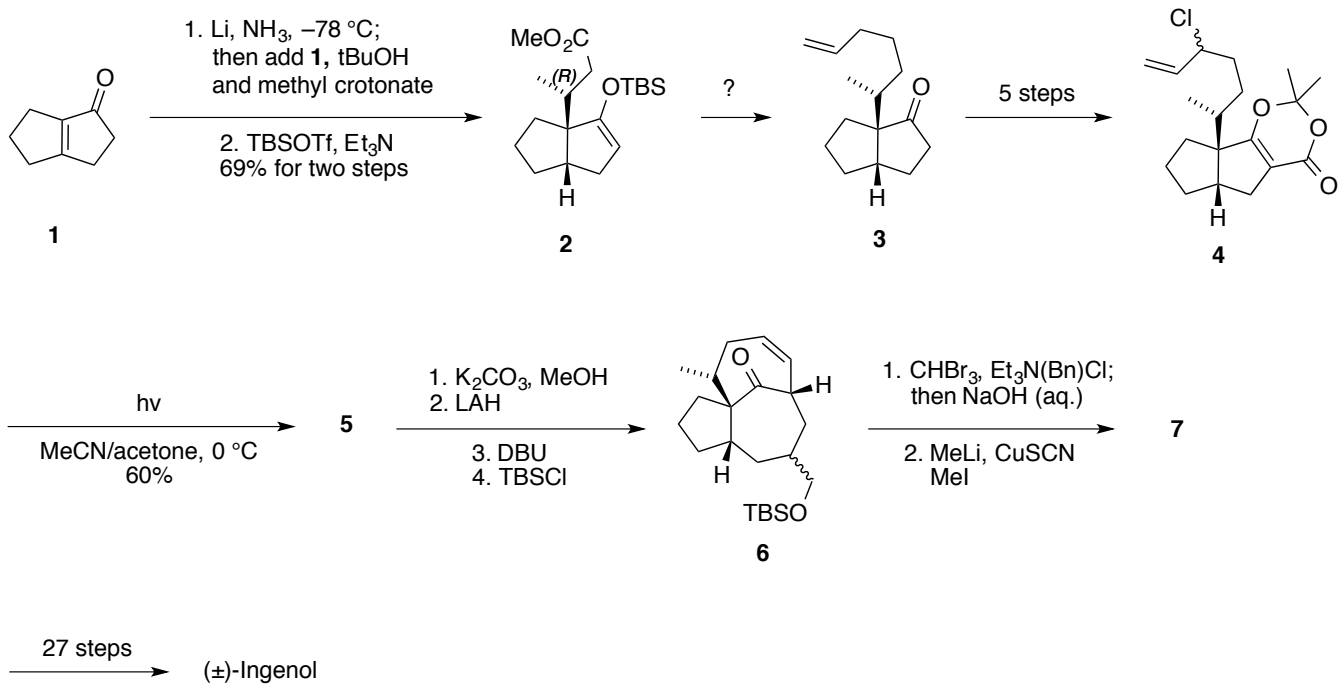
Submitted by Samuel Rieder

First Total Synthesis of (±)-Ingenol

Problem:

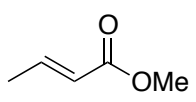


1. Propose a mechanism for the transformation from **1** to **2** and explain the high stereoselectivity of the Micheal reaction ((*R*):(*S*) =14:1).

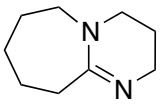
2. Propose conditions for the formation of **3** starting from the alcohol derived from the ester of **2**. (3 steps)

3. Give the structure of cycloheptanes **5** and **7.** (What is the role of $Et_3N(Bn)Cl$ in the reaction from **6** to **7**?)

4. Propose a mechanism for the transformation of the photoadduct **5** to **6**.



methyl crotonate



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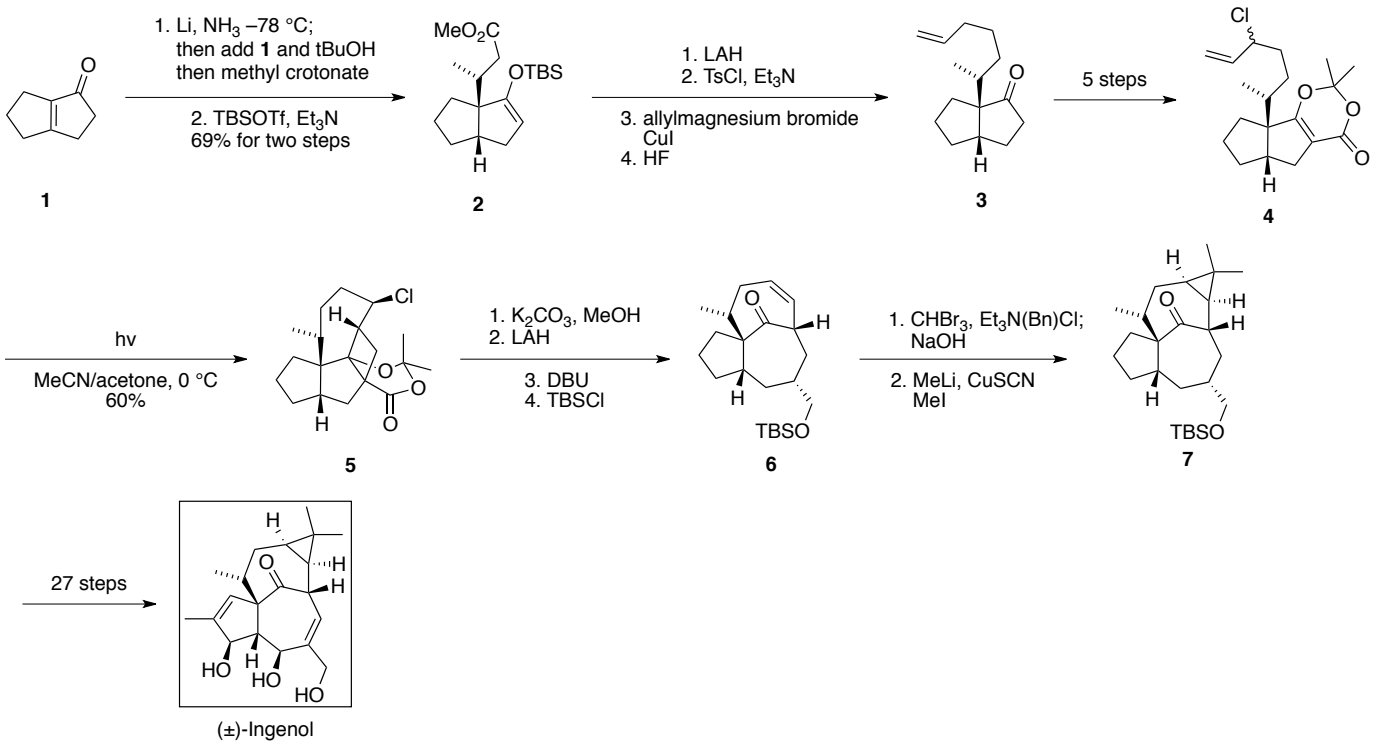
Solution:

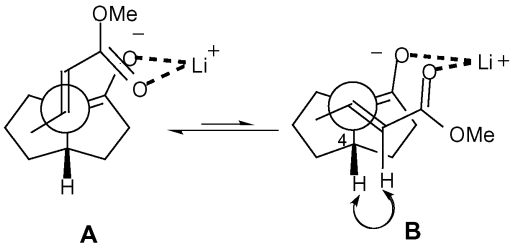


Comments:

1. Selectivity of the Michael reaction:

The *cis* configuration of the rings resulted from addition of the crotonate to the sterically less hindered β face of the enolate derived from **1**.

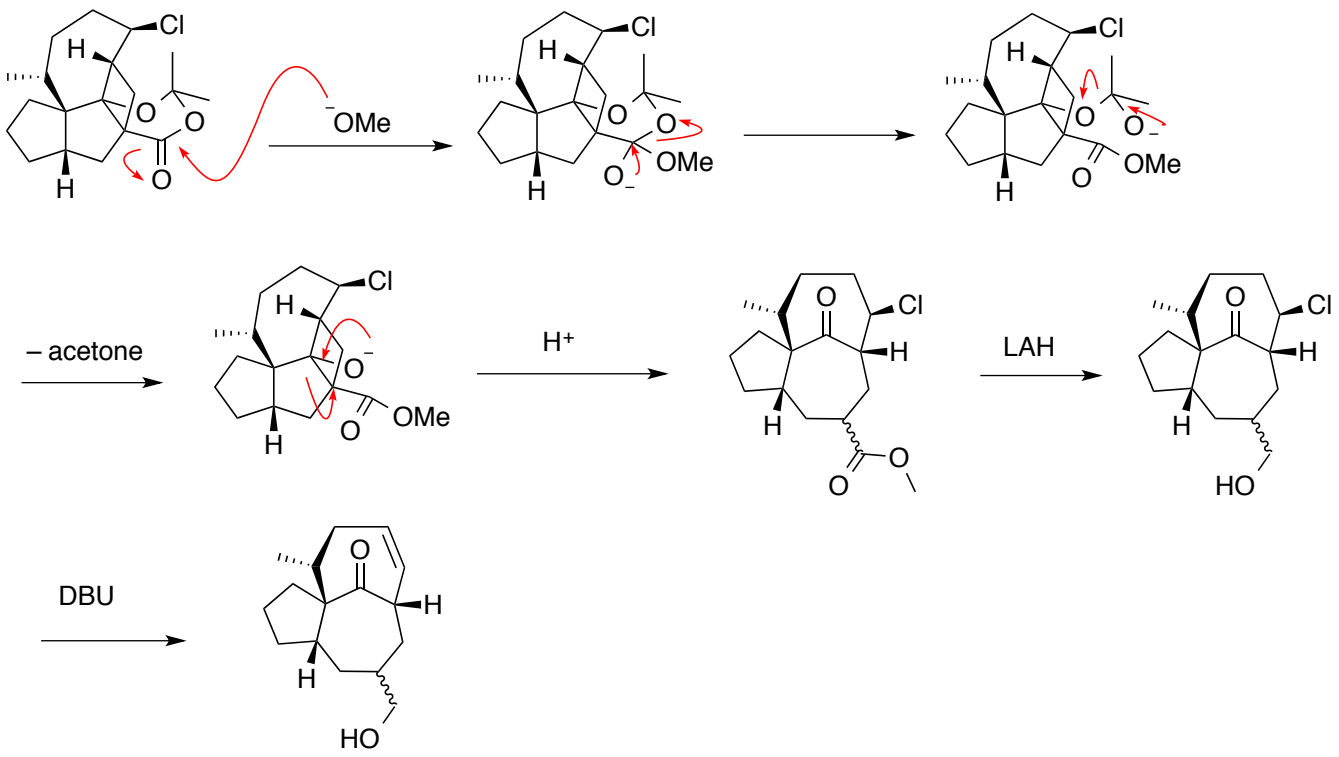
The stereochemical outcome can be rationalised by examination of the diastereomeric chelated transition state structures A and B (Heathcock-Seebach model).



While both A and B experience interactions between the crotonate and the enolate, conformer B also suffers from an unfavourable steric interaction between the crotonate α-proton and the C-4 methine of the enolate leading to the preferential formation of **2** from conformer A.

3. Phase Transfer Catalyst

4.



References:

J. D. Winkler, M. B. Rouse, M. F. Greaney, S. J. Harrison, Y. T. Jeon, *J. Am. Chem. Soc.* **2002**, *124*, 9726–9728.

J. D. Winkler, S. J. Harrison, M. F. Greaney, M. B. Rouse, *Synthesis* **2002**, 2150–2154.